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Insights on CRISPR/Cas-Based Fungal Genome Engineering Developments and Challenges over Secondary Metabolite Production

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Description

Fungi are an important source of bioactive secondary metabolites (SMs), which have numerous applications in medicine, agriculture, human health, and a variety of other industries. The genes involved in SM biosynthesis are typically grouped together in a region known as a biosynthetic gene cluster (BGC). The recent development of numerous genetic and genomic technologies has aided in the identification of many cryptic or uncharacterized BGCs and their associated SMs. However, many obstacles continue to obstruct the broad exploration of industrially important secondary metabolites. The recently developed CRISPR/Cas system has transformed fungal genetic engineering and enabled the discovery of novel bioactive compounds.

In this review, we first introduce fungal BGCs and their relationships with associated SMs, followed by a brief summary of traditional fungal genetic engineering strategies [1-3]. Following that, we present a variety of cutting-edge CRISPR/Cas-based tools that have been developed, as well as a review of recent applications of these methods in fungi for research on the biosynthesis of SMs. Finally, the challenges and limitations of these CRISPR/Cas-based systems are discussed, and future research directions for expanding their applications and improving efficiency for fungal genetic engineering are proposed.

Fungi are a major source of secondary metabolites (SMs), which are defined as a wide range of low-molecular-weight organic compounds synthesized from simple and inorganic precursors. SMs do not directly participate in growth and development; instead, they provide a selective advantage that promotes the survival and fitness of the producing organism. Although many fungi-derived SMs have been identified, many SMs remain unknown. So far, approximately 120,000 fungal species have been identified; however, this figure represents less than 8% of the estimated total number of fungal species on the planet. Furthermore, due to the technical challenges of discovering and identifying novel SMs, only a small percentage of SMs have been identified from fungi. In the fungal genome, the genes responsible for SM biosynthesis are typically clustered together in the form of biosynthetic gene clusters (BGCs).

A fungal biosynthetic gene cluster (BGC) usually contains genes encoding core synthases/synthatases, biosynthetic tailoring enzymes, regulators, and transporters, as well as self-resistance enzymes [4,5]. Because of the rapid development of advanced sequencing technologies and genomic tools, the number of publicly available fungal genomes has skyrocketed in recent years. With the help of concurrently developed automated genome mining tools such as antiSMASH, MIBiG 2.0, and BiG-SCAPE, this accumulation of annotated genomic information has accelerated the identification of BGCs. Robey et al. discovered that the number of BGCs encoded by each fungal genome varied greatly between species by performing bioinformatic analysis on 1037 fungal genomes. Furthermore, BGCs range in size from a few kb (containing two genes) to 100 kb. (containing up to 27 genes). We know very little about the relationship between fungal BGCs and their associated SMs, not only because many well-characterized BGCs are transcriptionally silent, but also because a large number of BGCs have yet to be investigated for their biosynthetic potential.

Thus, activating silent BGCs and exploring novel BGCs in the fungal kingdom is a prerequisite for identifying novel SMs. Environmental signals, global regulators, cluster-specific transcription factors (TFs), and epigenetic factors have all been shown to regulate BGC expression in fungi. Crosstalk and interactions between these factors have been observed during the biosynthesis of fungal secondary metabolites. Environmental signals and global regulators typically have a regulatory effect on the transcription of multiple BGCs, whereas cluster-specific regulators/TFs typically regulate only one BGC. Some BGCs' expression is specifically controlled by cluster-specific TFs, and the levels of these TFs' expression are closely related to BGC activation. Promoter replacement or TF overexpression appear to be effective in activating a previously silent BGC for TFs with weak native promoters. In *Aspergillus terreus*, for example, promoter replacement of the cluster-specific transcriptional factor ATEG_06205 resulted in the activation of a polyketide biosynthesis gene cluster and the production of highly pigmented naphthoquinones.

The Tet-on system was used to activate the taz pathway and induce the production of novel azaphilones in A. terreus by overexpressing the pathway-specific transcription factor tazR. Epigenetic regulation, which affects gene activity in a variety of ways, includes DNA methylation rewriting, histone modification, small RNA expression, and modulation of high-order chromatin structures. In fungi, epigenome reprogramming is emerging as a promising strategy for altering BGC activity and promoting SM biosynthesis. Some BGCs, however, are active under certain conditions. To identify SMs regulated by these active BGCs, knock-out strains are typically generated via gene deletion or disruption, followed by metabolite profiling. The investigation of BGC expression regulatory mechanisms and their links to SM biosynthesis provides a theoretical foundation for the design and evaluation of practical strategies for SM production from fungi.

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Conflict of Interest

Authors declare no conflict of interest.

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